

Synthesis of (2*S*,5*S*)-*trans*-5-(4-fluorophenoxymethyl)-2-(1-*N*-hydroxy ureidyl-3-butyn-4-yl)-tetrahydrofuran — (CMI-977)*

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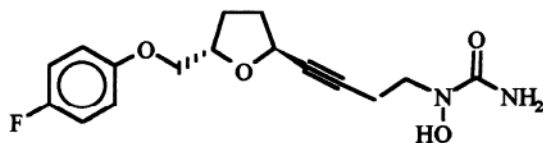
Abstract: Three novel, versatile and cost-effective syntheses of the title compound, a potent 5-LO inhibitor, have been described.

Asthma is a chronic inflammatory disease complicated by periodic acute inflammatory changes. Morphologically, asthma is characterised by infiltration of the bronchial mucosa and epithelium with activated T cells, mast cells, eosinophils, neutrophils and macrophages. The complexity of the interactions between these and other inflammatory cells, and the interactions between the pro-inflammatory mediators which they secrete, remains to be fully elucidated. In the past the conventional view has been that targeting a single group of mediators for pharmacological blockade would be unlikely to confer significant benefit. This view, however, is not compatible with the evidence generated in the past decade regarding the unexpectedly high efficacy in clinical trials of drugs that block the synthesis or the activity of the leukotriene mediators.

Leukotrienes (LT) are metabolites of arachidonic acid produced by the activity of 5-lipoxygenase (5-LO). Arachidonic acid is presented to the 5-LO enzyme by 5-lipoxygenase-activating protein, a cofactor resident in the nuclear membrane; the interaction leads to the formation of the unstable intermediate, leukotriene A₄. LTA₄ is further converted either to the chemotaxin LTB₄ by LTA₄ hydrolase, or to LTC₄ by the transmembrane enzyme LTC₄ synthetase. Further conversion of LTC₄ to LTD₄ and then to LTE₄ occurs by the action of enzymes ubiquitous in both tissues and circulation.

The cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄ are produced by a variety of inflammatory cells including eosinophils, mast cell, macrophages, monocytes and basophils. Their physiological effects mimic the recognized pathophysiological features of asthma, in particular, bronchoconstriction, increased airways responsiveness, increased microvascular permeability and hypersecretion of mucus [1]. These activities are mediated through an interaction between the agonist and specific cell-surface receptors.

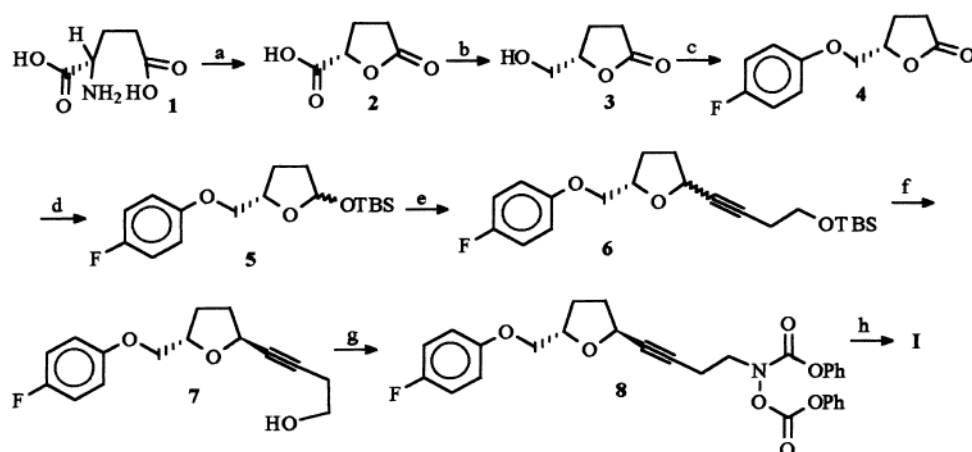
CMI-977 (Scheme 1) is a potent 5-LO inhibitor that blocks the production of leukotrienes and is currently being developed for the prophylactic treatment of chronic asthma [2]. It is a single enantiomer with an all *trans* (2*S*, 5*S*) configuration; the tetrahydrofuran moiety is diversely substituted. Inhibition of



Scheme 1 CMI-977 (I). (2*S*,5*S*)-*trans*-5-(4-Fluorophenoxymethyl)-2-(1-*N*-hydroxy-ureidyl-3-butyn-4-yl)-tetrahydrofuran.

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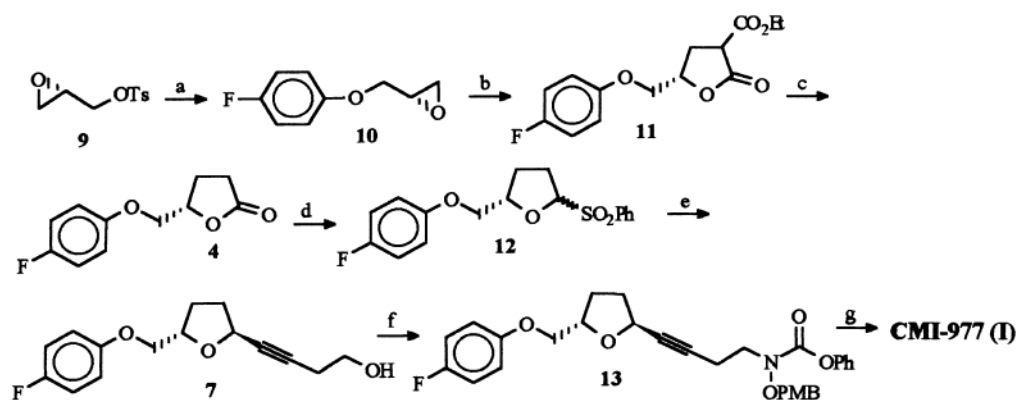
Scheme 2 Reagents: (a) HNO_2 , (b) $\text{BH}_3 \cdot \text{Me}_2\text{S}$, (c) 4-Fluorophenol, Ph_3P , DIAD, (d) (i) DIBAL (ii) TBSCl, Imid., DMAP, (e) (i) TMSBr (ii) $n\text{-BuLi}$, $\text{HC}\equiv\text{C}(\text{CH}_2)_2\text{OTBS}$, (f) (i) TBAF (ii) separation of *trans* from *trans/cis* isomers by crystallization (g) PhOCONHOCOOPh , Ph_3P , DIAD, (h) NH_4OH .

LTB_4 production in ionophore stimulated human whole blood was employed in the evaluation of all possible chiral isomers of CMI-977; of the four isomers, the *S,S* isomer was found to have the best potency and was selected for further development.

The discovery route [3] for synthesis of CMI-977 is delineated in Scheme 2. This route was plagued with several problems that mitigated against efficient scale-up and cost-effective production of the target molecule.

Many reactions necessitated cryogenic conditions; silyl protecting groups were used in numerous instances. The atom economy in the protection-deprotection sequence was not in the desired direction and led to a large waste stream that was difficult to handle. Many reagents were expensive and unstable towards extended storage and shipping. Subsequently, during the crucial C–C coupling, with $n\text{-BuLi}$ a 50% mixture of *trans/cis* isomers was obtained whose separation to furnish the desired *trans* material involved tedious chromatography.

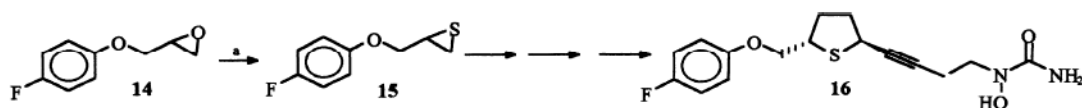
The problems encountered hitherto prompted us to undertake route selection efforts to devise novel, cost-effective syntheses of CMI-977 that would be amenable to scale up and large scale production. We therefore, developed three novel routes to the target molecule that obviated the problems cited above. The first route (Scheme 3) promises to be efficacious and offers the following advantages: (i) para-fluorophenol and glycidyl tosylate [4] are inexpensive and commercially available; the arylated lactone is obtained in high yield, (ii) the C–C coupling reaction [5] using a Grignard reaction yields the *trans-cis* alcohol in 70:30; the conversion of lactone (4) to the crystalline sulfone (12) dramatically increases the



Scheme 3 Reagents: (a) 4-Fluorophenol, NaH , (b) $\text{CH}_2(\text{CO}_2\text{Et})_2, \text{Na}$, (c) DMA, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, (d) (i) DIBAL (ii) PhSO_3H , CaCl_2 , (e) (i) $i\text{PrMgBr}$, $\text{HC}\equiv\text{C}(\text{CH}_2)_2\text{OTHP}$, ZnBr_2 (ii) 1% HCl (iii) crystallizations, (f) PhOCONHOPMB , Ph_3P , DEAD, (g) (i) NH_3 (ii) $\text{BF}_3 \cdot \text{OEt}_2$.

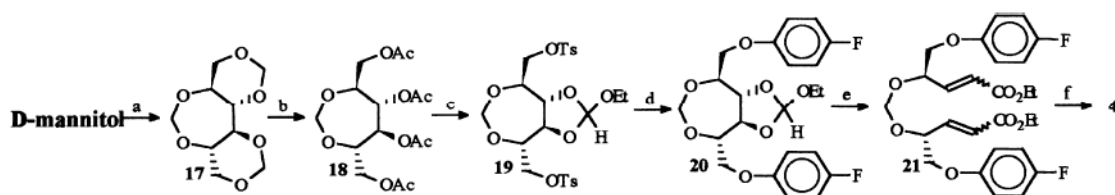
efficiency of the reaction, (iii) all cryogenic reactions have been circumvented while the silyl protecting groups have been replaced with alternates making the reactions operationally facile.

Route 1 has been readily adapted to the synthesis of the thio analogue of CMI-977 (**16**) by converting **14** into a thioglycidyl ether **15** (Scheme 4) followed by repeating the sequence of reactions as described in Scheme 3.



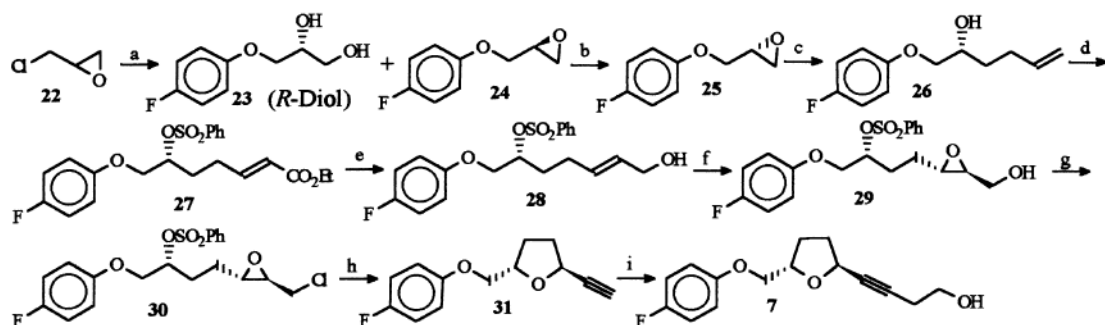
Scheme 4 Reagents: (a) $(\text{NH}_2)_2\text{CS}$, MeOH.

An alternative synthesis of CMI-977 from D-mannitol [6] is described in Scheme 5. The C-2 axis of symmetry of the precursor (**21**) furnishes two molecules of the fluorinated lactone on cleavage. All reactions occur at ambient temperatures under extremely mild conditions. Further transformation of the fluorolactone proceeds as described under Scheme 5.

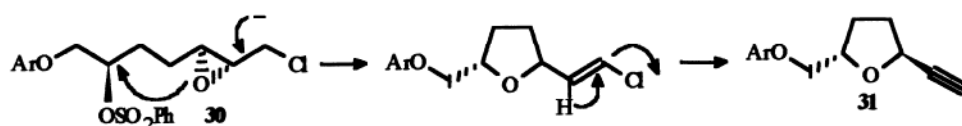


Scheme 5 Reagents: (a) CH_2O , conc. HCl, (b) Ac_2O , AcOH, H_2SO_4 , (c) (i) NaOMe (ii) TsCl, Py (iii) $(\text{EtO})_3\text{CH}$, PTSA, (d) 4-Fluorophenol, aq. KOH, (e) (i) 1% aq. HCl (ii) LTA (iii) $\text{Ph}_3\text{P}:\text{CHCO}_2\text{Et}$, (f) (i) Pd/C, H_2 (ii) 10% aq. H_2SO_4 .

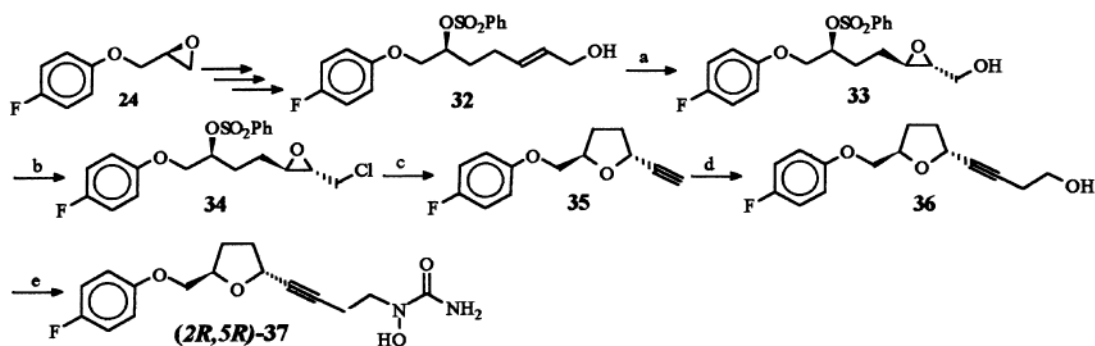
Route iii (Scheme 6) is stereoselective and leads to the exclusive formation of the *trans* product. A fascinating feature of this route is the transformation of intermediate (**30**) to the alcohol (**7**) [7]. A plausible mechanism is postulated in Scheme 7. Our chemistry is broadly applicable to the formation of the 5,6,7 membered ring and other heteroatom analogues by suitable manipulations of the reagents and substrates. The same sequence of reactions has also been adapted for the preparation of CMI-983 (**37**) (an enantiomer of CMI-977) (Scheme 8).



Scheme 6 Reagents: (a) (i) 4-Fluorophenol, K_2CO_3 (ii) Hydrolytic kinetic resolution (*R,R*) Jacobsen cat., H_2O (b) (using diol) (i) TsCl, Py (ii) NaH, (c) Mg, AllylBr, CuCN, (d) (i) PhSO_4Cl , Et_3N , DMAP (ii) O_3 , DMS (iii) $\text{Ph}_3\text{P}:\text{CHCO}_2\text{Et}$, (e) DIBAL, (f) Sharpless Asymmetric Epoxidation, (g) Ph_3P , $\text{CCl}_4:\text{CHCl}_3$, NaHCO_3 , (h) LDA (i) *n*-BuLi, $\text{BF}_3\cdot\text{OEt}_2$, ethylene oxide.



Scheme 7



Scheme 8 Reagents: (a) Sharpless Asymmetric Epoxidation (b) TPP, CCl_4 , (c) LDA, (d) *n*-BuLi, Ethylene oxide, $\text{BF}_3 \cdot \text{OEt}_2$, (e) (i) PhOCONHOCOPh , PPh_3 , DEAD (ii) NH_4OH .

CONCLUSION

The routes described herein are currently being optimised for production of multi-kilo quantities of the target molecule.

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